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Palladium-Catalyzed Domino Cyclization (5-*exo*/3-*exo*), Ring-Expansion by Palladium Rearrangement, and Aromatization: An Expedient Synthesis of 4-Arylnicotinates from Morita–Baylis–Hillman Adducts

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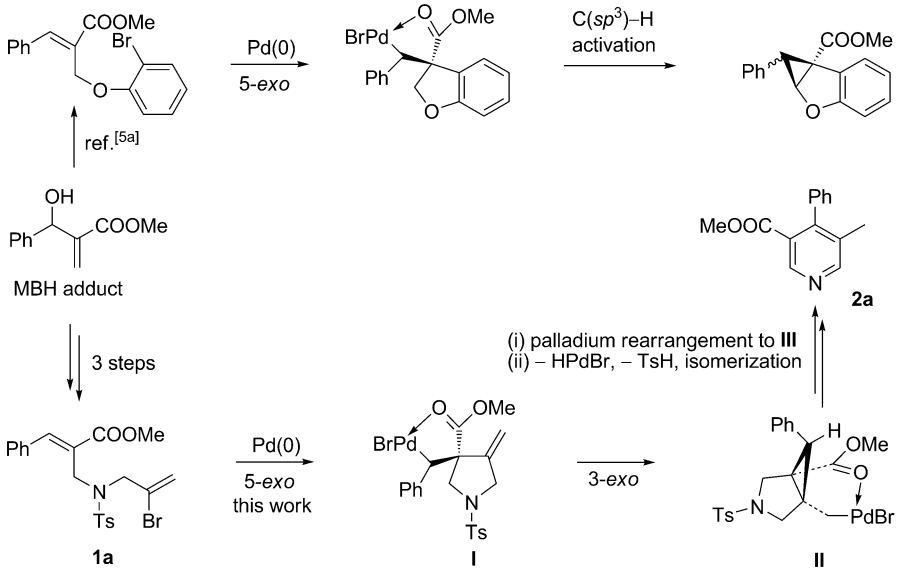
Abstract: Various 4-arylnicotinate derivatives were synthesized *via* a palladium-catalyzed cascade reaction of *N*-(2-bromoallyl)-*N*-cinnamyltosylamides in a one-pot procedure in good yields. The reaction involves a domino 5-*exo*/3-*exo* carbopalladation, ring-expansion by palladium rearrangement, and an aromatization process.

Keywords: 4-arylnicotinates; Morita–Baylis–Hillman adducts; palladium; palladium rearrangement; pyridines

Polysubstituted pyridines are an important class of compounds due to their abundance in biologically important natural substances and their usefulness as synthetic intermediates in organic synthesis.[1] Especially, the synthesis of functionalized pyridines with a carboxylic acid moiety at the 3-position (nicotinic acid derivatives) has received much attention due to their biological importance.[2] The Morita–Baylis–Hillman (MBH) adducts have been used for the synthesis of various biologically important substances and synthetic intermediates.[3] Various efficient protocols for the synthesis of pyridine and quinoline derivatives from the MBH adducts have also been developed by us and other groups.[4]

In 2008, we reported the synthesis of 6-oxacyclopropa[*a*]indenes *via* a palladium-catalyzed sequential 5-*exo* carbopalladation and C(sp^3)–H activation from modified MBH adduct bearing a 2-bromoaryl moiety, as shown in Scheme 1.[5a] The alkylpalladium inter-



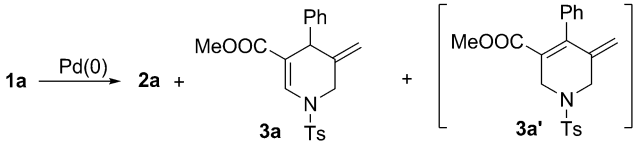
Scheme 1. Synthetic rationale of methyl nicotinate **2a**.

mediate does not have a suitable β-hydrogen atom and activates the proton near to the oxygen atom of the dihydrobenzofuran ring to form a cyclopropane ring. Later, we observed a similar 5-*exo* carbopalladation of modified MBH adducts in their palladium-catalyzed domino reactions.[5b,c] In 1992, the 2010 Nobel prize laureate Negishi and his co-workers rationalized that palladium-catalyzed cyclizations of 2-halo-1,6-dienes occur as sequences of 5-*exo*/3-*exo* carbopalladations with subsequent palladium rearrangement of the cyclopropylcarbinyl-palladium intermediate in which the β-H elimination is suppressed.[6a] Later, such a domino 5-*exo*/3-*exo* carbopalladation accompanying a palladium rearrangement process was studied by many research groups including those of Stevenson,[6b] de Meijere,[6c–e] and Ahn.[6f] Similar *n*-*exo*(*n*=6 or 4)/3-*exo* carbopalladation and palladium rearrangements have also been reported.[7] Such a tandem 5-*exo*/3-*exo* cyclization accompanying ring-expansion process was also observed in a radical reaction of a propargyl ether of an MBH adduct[8a] and bis-vinyl ethers.[8b] In these respects, we envisioned that 3,4,5-trisubstituted pyridine derivative **2a** could be synthesized from **1a** *via* a palladium-catalyzed domino cyclization (5-*exo*/3-*exo*), ring-expansion by palladium rearrangement, and an aromatization process, as shown in Scheme 1.

The starting material **1a** was prepared readily from the MBH adduct of benzaldehyde and methyl acrylate by a simple three-step process, that is a sequential bromination, substitution with tosylamide, and 2-bromoallylation (see the Supporting Information). With **1a** in our hand, a brief screening of the reaction conditions was carried out for the synthesis of methyl nicotinate **2a**, and the results are summarized in Table 1. When we carried out the reaction in the presence of Et_3N (entries 1–3), 1,4,5,6-tetrahydropyridine **3a** was produced as a major product along with a trace amount of 1,2,5,6-tetrahydropyridine **3a′** (<4%).[6a] The reaction in the presence of K_2CO_3 afforded a low yield of **2a** (10%), but the major product was still **3a** (entry 4). In order to facilitate the elimination of *p*-toluenesulfinic acid from **3a** or **3a′**, we examined the reaction with Cs_2CO_3 (entry 5), and **2a** was obtained in good yield (65%). The reaction in refluxing CH_3CN was not efficient even in the presence of Cs_2CO_3 for a long time (entry 6).

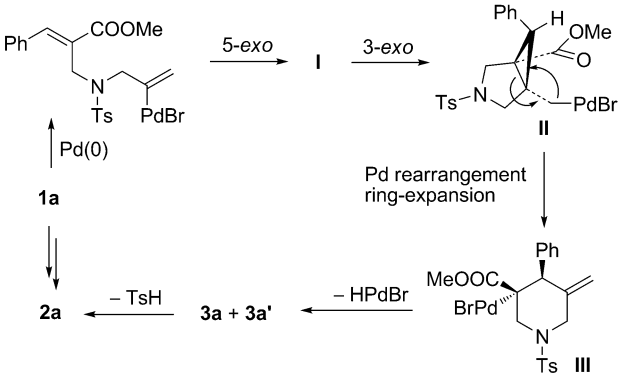
The mechanism for the formation of **2a** could be proposed in detail, as shown in Scheme 2. An oxidative addition of the C–Br bond of **1a** to Pd(0) and a subsequent 5-*exo* carbopalladation gave an alkylpalladium intermediate **I**. Because the intermediate **I** has no suitable β-hydrogen atom that can be eliminated, a sequential 3-*exo* carbopalladation occurred to afford an alkylpalladium intermediate **II**. The presence of an ester group can stabilize both alkylpalladium intermediates **I** and **II** by chelation,[7a,9] and this

Table 1. A brief optimization of reaction conditions.[a]



Entry	Base	Solvent	Time [h]	**2a** [%]	**3a** [%]
1	Et_3N[b]	DMF[d]	20	0	54[g]
2	Et_3N[b]	DMF	3	0	72[g]
3	Et_3N[b]	DMF[e]	3	<5	76[h]
4	K_2CO_3[c]	DMF	3	10	74[h]
5	Cs_2CO_3[c]	DMF	3	**65**	0
6	Cs_2CO_3[c]	CH_3CN[f]	10	12	70[h]

[a] *Conditions:* substrate **1a** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), 120 °C.
[b] 2.0 equiv.
[c] 2.5 equiv.
[d] At 70 °C.
[e] NaI (1.0 equiv.) was added.
[f] Reflux.
[g] **3a′** was isolated in 4%.
[h] Trace amount of **3a′** was observed but not isolated.

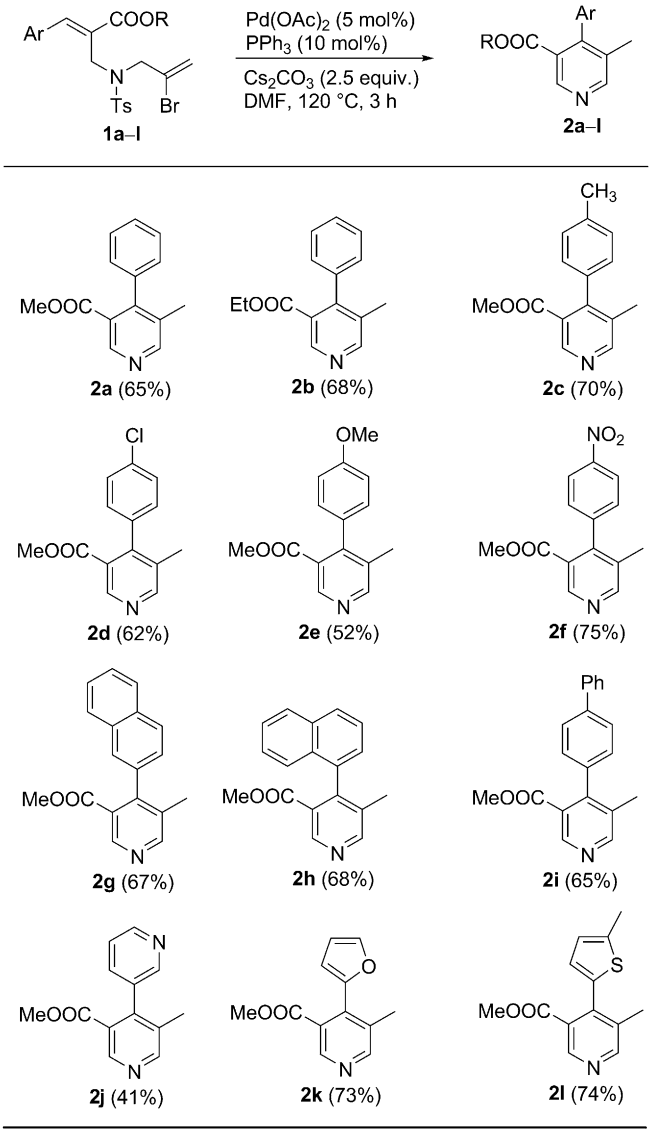


Scheme 2. A plausible reaction mechanism.

stabilization effect might facilitate the 5-*exo*/3-*exo* cascade carbopalladations. The intermediate **II** has no β-hydrogen atom, thus a concomitant palladium rearrangement/ring expansion proceeded to form a piperidine intermediate **III**. A subsequent *syn* β-H elimination of **III** could occur in either direction; however, 1,4,5,6-tetrahydropyridine **3a**[10] was formed as a major product along with a trace amount (<4%) of 1,2,5,6-tetrahydropyridine **3a′**.[11] The reason for the selective formation of **3a** is not clear at this stage; however, the ratio of **3a**/**3a′** might be dependent on the dihedral angles between the C–Pd bond and two C–H bonds. A subsequent elimination of TsH from **3a**/**3a′** and double bond isomerization furnished **2a**.

Encouraged by these successful results, *N*-(2-bromoallyl)-*N*-cinnamyltosylamides **1b–l** were prepared from the corresponding MBH adducts (see the Sup-

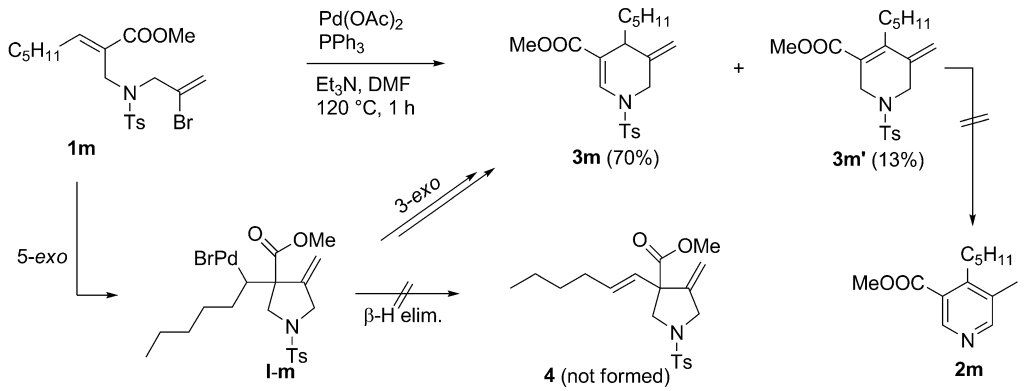
Table 2. Synthesis of various 4-arylnicotinates.



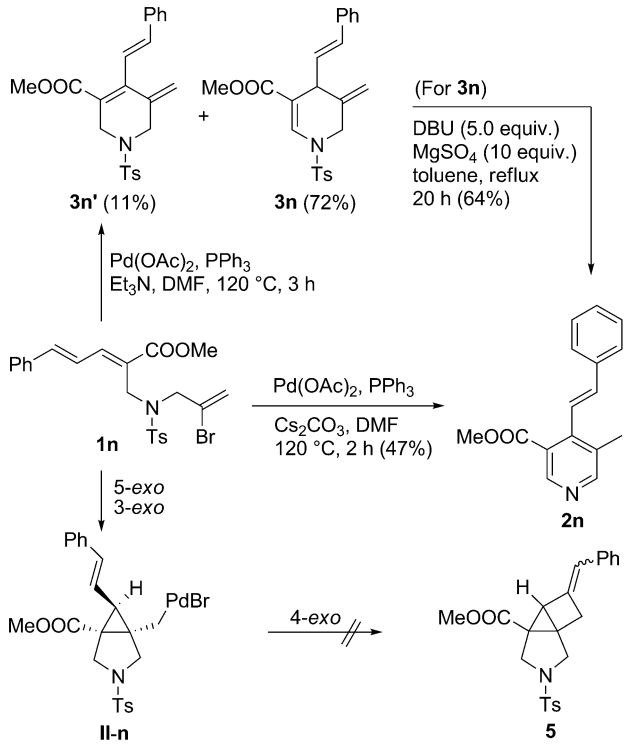
porting Information), and examined the synthesis of 4-arylnicotinates. As summarized in Table 2, various 4-arylnicotinates **2b–l** were synthesized in moderate to good yields (41–75%) in a one-pot procedure under the optimized palladium-catalyzed reaction conditions.

As a next experiment, we examined the reaction of *n*-pentyl derivative **1m** in order to prepare 4-pentylnicotinate **2m**, as shown in Scheme 3. However, the reaction of **1m** under the optimized condition using Cs_2CO_3 in DMF showed the formation of **3m**/**3m′** in low yield along with many intractable side products. The reaction of **1m** under the influence of Et_3N afforded **3m** (70%) along with a low yield of **3m′** (13%). A desired 4-pentylnicotinate **2m** was not formed during the reaction at all. Thus the conversion of **3m** to **2m** was examined under various conditions; however, we failed to obtain **2m** even under conditions employing an excess amount DBU (5.0 equiv.) in refluxing toluene (*vide infra*). The proton at the 4-position of **3m** is less acidic than those of the corresponding 4-aryl derivatives producing **2a–l**, and this might be the reason for the failure. It is noteworthy that the 3-*exo* carbopalladation/palladium rearrangement process occurred at the intermediate stage **I-m** to give **3m**/**3m′** preferentially rather than the β-H elimination to form 3-hex-1-enylpyrrolidine derivative **4**.

In order to synthesize 4-styrylnicotinate **2n** we examined the reaction of **1n**, as shown in Scheme 4. The one-pot synthesis of **2n** was carried out under the optimized condition in the presence of Cs_2CO_3; however, the yield of **2n** was moderate (47%). Thus we examined a two-step process, the synthesis of tetrahydropyridine and the following aromatization. The tetrahydropyridine **3n** was obtained in good yield (72%) along with **3n′** (11%) when we carried out the reaction in the presence of Et_3N. The intermediate **3n** could be converted to **2n** under the influence of DBU (5.0 equiv.) in refluxing toluene in good yield (64%). However, the overall yield of **2n** using a two-step process was similar to that of the one-pot reaction. A consecutive 4-*exo* carbopalladation at the intermediate stage **II-n** to a tricyclic compound **5** cannot occur



Scheme 3. Attempted synthesis of 4-pentylnicotinate **2m**.



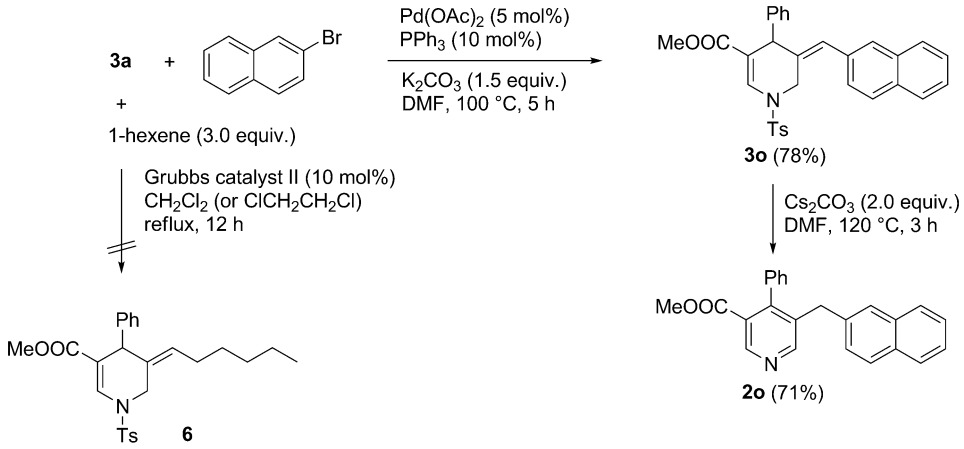
Scheme 4. Synthesis of 4-styrylnicotinate **2n**.

because the alkylpalladium and styryl moieties are positioned in a *trans*-relationship.

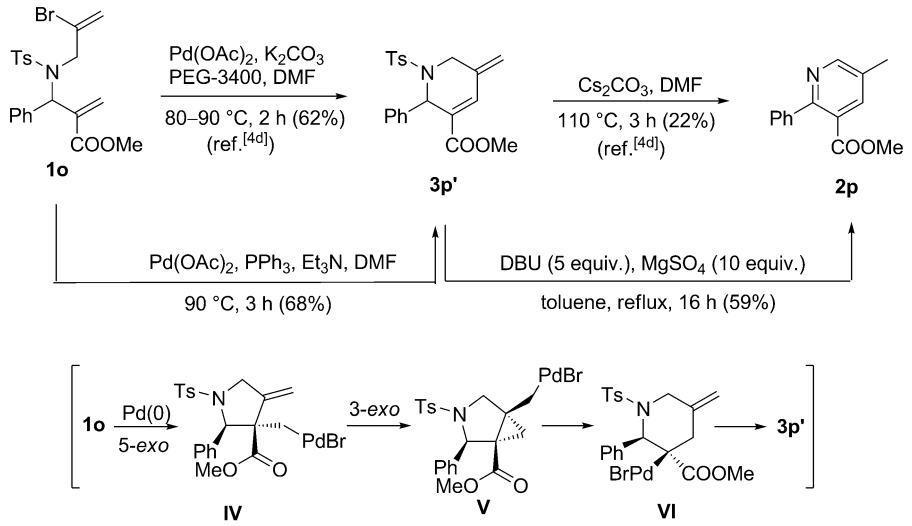
In order to synthesize 5-arylmethyl- or 5-alkylnicotinates, we examined a palladium-catalyzed Heck reaction of **3a** and cross-metathesis (CM) reaction, as shown in Scheme 5. The Heck reaction of **3a** with 2-bromonaphthalene was carried out under the influence of K_2CO_3, because compound **3a** could be converted into **2a** in the presence of Cs_2CO_3. In this way, a tetrahydropyridine **3o** was obtained in good yield (78%) along with a trace amount of pyridine **2o** (3%). The tetrahydropyridine **3o** could be converted to **2o** in good yield (71%) by treatment with Cs_2CO_3 in DMF at 120 °C for 3 h. However, a trial for the conversion of methylene derivative **3a** to hexylidene derivative **6** by a CM reaction with 1-hexene failed in the presence of a second generation Grubbs catalyst.[12]

2-Arylnicotinate **2p** could also be synthesized from *N*-(2-bromoallyl)-substituted aza-MBH adduct **1o**, as shown in Scheme 6. The synthesis of 1,2,5,6-tetrahydropyridine **3p′** was reported by us a few years ago.[4d] At that time, the aromatization of **3p′** afforded only a low yield of **2p** (22%). Thus we reexamined a one-pot synthesis of **2p** from **1o** in the presence of Cs_2CO_3 in DMF. At the early stage of the reaction compound **3p′** was formed as a major product along with a trace amount of **2p**; however, a prolonged heating of the reaction mixture caused a severe decomposition of **3p′** without an increase of **2p**. To our delight, the aromatization of **3p′** was efficiently conducted with DBU to produce **2p** in moderate yield (59%), as for the conversion of **3n** to **2n** (*vide supra*, Scheme 4). It is interesting to note that **3p′** has been formed as the sole product, as compared to the formation of **3a** and **3a′** in a mixture from **1a** (*vide supra*, Scheme 2). As shown in Scheme 6, the first 5-*exo* carbopalladation might occur selectively towards the *re*-face of the double bond of **1o** to form the intermediate **IV**, presumably due to the electronic repulsion between the ester and *N*-sulfonyl groups. The intermediate **IV** was converted to **VI**, and a subsequent syn β-H elimination produced **3p′**.

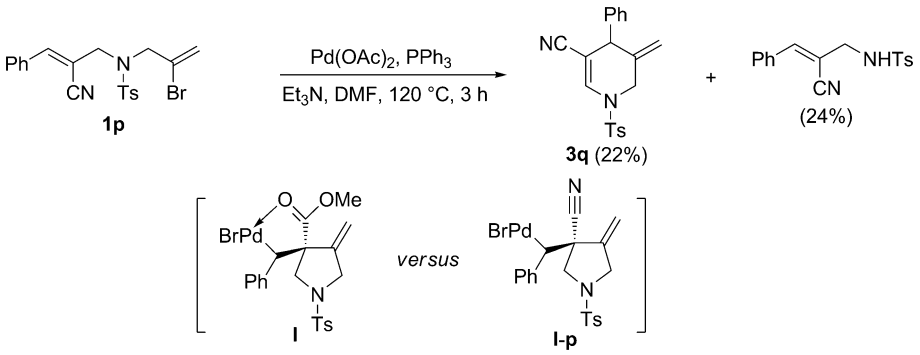
As a next examination, we carried out the reaction of **1p** bearing a nitrile group instead of an ester, as shown in Scheme 7. A severe decomposition was observed under the conditions employing Cs_2CO_3 in DMF at 120 °C, while the use of Et_3N at low temperature (90 °C) showed very sluggish reactivity. Only a low yield of tetrahydropyridine **3q** (22%) was ob-



Scheme 5. Heck reaction of **3a** and an extension of side chain.



Scheme 6. Synthesis of 2-phenylnicotinate **2p**.

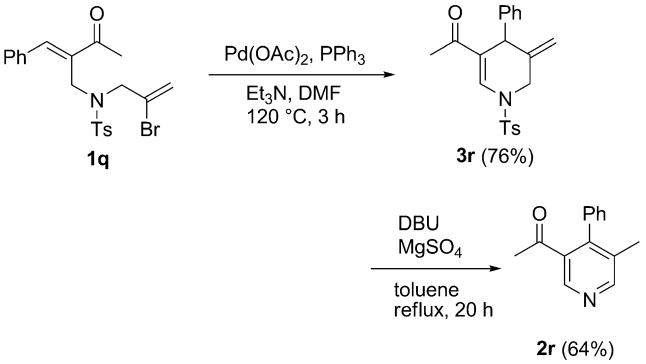


Scheme 7. The importance of a directing group.

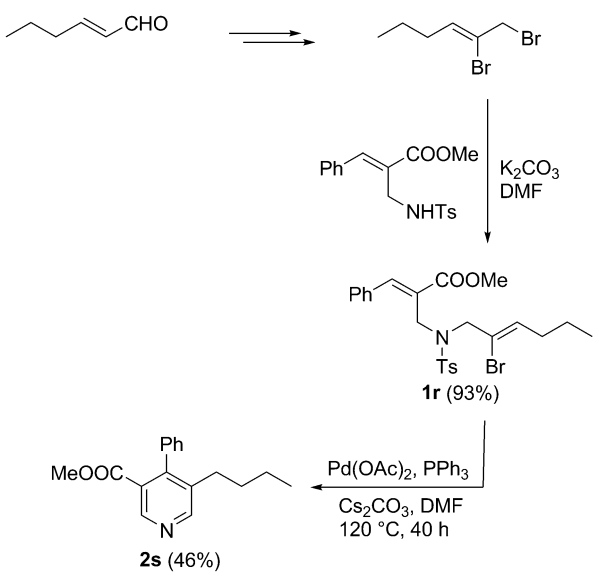
tained along with a tosylamide derivative (24%) when we carried out the reaction under the influence of Et_3N at 120 °C. As we noted above, the ester moiety of **1a** might facilitate 5-*exo* carbopalladation by stabilizing the alkylpalladium intermediate **I**; however, such a directing and/or stabilizing effect is not present in the corresponding intermediate **I-p** for the nitrile derivative, and this would be the reason for the low yield of **3q**.

In order to obtain 3-acetylpyridine **2r** the reaction of an acetyl derivative **1q** was examined, as shown in Scheme 8. Initially, we examined a one-pot synthesis of **2r** in the presence of Cs_2CO_3 in DMF at 120 °C; however, we failed to obtain **2r** in a reasonable yield. Monitoring of the reaction progress showed a rapid formation of tetrahydropyridine **3r** as a major product along with a trace amount of **2r**. However, the amount of **2r** was not increased even after a prolonged heating. Thus, we prepared **3r** in the presence of Et_3N and examined the aromatization of **3r** to **2r**. As in the case of the styryl derivative (Scheme 4) an aromatization of **3r** to **2r** was carried out in the presence of DBU in toluene, and **2r** could be obtained in moderate yield (64%).

As a last entry, we examined the synthesis of 5-alkylnicotinate **2s**, as shown in Scheme 9. As noted above in Scheme 5, an attempted synthesis of 5-alkylnicotinate using the cross-metathesis protocol failed. Thus, we prepared compound **1r** with 1,2-dibromo-



Scheme 8. Synthesis of 3-acetylpyridine **2r**.



Scheme 9. Synthesis of 5-butylnicotinate **2s**.

hex-2-ene, which was prepared from *trans*-2-hexenal in three steps.[6b] The one-pot synthesis of 5-butylnicotinate **2r** was successfully carried out under the optimized conditions in reasonable yield (46%).

In summary, we have disclosed an efficient synthesis of various nicotinate derivatives from suitably modified Morita–Baylis–Hillman (MBH) adducts *via* a palladium-catalyzed reaction involving domino 5-*exo*/3-*exo* carbopalladations, ring-expansion by palladium rearrangement, and an aromatization process.

Experimental Section

Typical Experimental Procedure for the Pd-Catalyzed Synthesis of Methyl 4-Phenyl-5-methylnicotinate (2a)

A mixture of **1a** (232 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 5 mol%), PPh_3 (13 mg, 10 mol%) and Cs_2CO_3 (408 mg, 2.5 equiv.) in DMF (1.5 mL) was heated to 120 °C for 3 h. The reaction mixture was poured into dilute HCl solution and extracted with diethyl ether. The organic solvent was removed by evaporation, and the residue was purified by flash column chromatography (hexanes/ether, 3:1) to afford **2a** as a pale yellow solid; yield: 125 mg (65%); mp 48–49 °C; IR (KBr): $\nu = 1734$, 1303, 1148 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.11$ (s, 3H), 3.62 (s, 3H), 7.15–7.17 (m, 2H), 7.36–7.48 (m, 3H), 8.62 (br s, 1H), 8.92 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 17.27$, 52.07, 126.39, 127.59, 127.77, 128.23, 132.11, 137.44, 148.39, 149.69, 153.26, 166.84; ESI-MS: $m/z = 228$ $[M+H]^+$; anal. calcd. for $C_{14}H_{13}NO_2$: C 73.99, H 5.77, N 6.16; found: C 74.13, H 5.89, N 6.01.

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